## REMARKS

This submission is in response to the final Office Action mailed May 7, 2008. Claim 16 remains pending. Claims 1-15 have been cancelled. No new matter has been introduced by way of this amendment. Reconsideration is respectfully requested.

Claim 16 stands rejected as obvious under 35 U.S.C. § 103(a) over Sanchez (FEBS Letters, 1998, c.436, p. 6-10) in view of Uesugi (Acta Neuropath., 1998, v. 9, pp. 351-356). According to the Examiner, Sanchez discloses that THC induces apoptosis in C6 glioma cells. and Uesugi teaches the use of a rat glioma cell line (C6) as a rat glioma model. In response to Applicants filed remarks, the Examiner notes that *in vitro* assays need not be 100% predictive of *in vivo* efficacy, which the Examiner remarks is not a standard for obviousness. The Examiner contends that the standard for obviousness is that one skilled in the art recognizes "that activity *in vitro* is reasonably predictive of *in vivo* activity" (emphasis in original). Applicants traverse the rejection and respectfully request reconsideration.

Applicants submit that the presently claimed invention is not obvious over the cited art. Contrary to the Examiner's interpretation, Applicants are not submitting that *in vitro* assays need be 100% predictive of *in vivo* efficacy as a standard for obviousness. Applicants submit that this assertion is a mischaracterization of Applicants previously submitted arguments. To clarify, Applicants submit that the Examiner has not met the burden of establishing a *prima facie* case of obviousness under 35 U.S.C. § 103(a) for the following reasons.

In light of the recent Supreme Court decision on *KSR International, Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1742 (2007), the USPTO issued a memorandum on May 3, 2007 from Margaret A. Focarino, Deputy Commissioner for Patent Operations, USPTO, to Technology Center Directors. A copy of this Memorandum is of record as previously submitted in the Response dated August 8, 2007.[1] As explained in the Memorandum, the Supreme Court reaffirmed the four (4) Graham factual inquiries to be considered in rendering an invention obvious. The factual inquiries are as follows:

(1) determining the scope and content of the prior art;

(2) ascertaining the differences between the prior art and the claims in issue;

(3) resolving the level of ordinary skill in the pertinent art; and

[1] Memorandum regarding the Supreme Court decision on *KSR Int'l. Co., v. Teleflex, Inc.*, from Margaret A. Focarino, Deputy Commissioner for Patent Operations, USPTO, to Technology Center Directors (May 3, 2007).

(4) evaluating evidence of secondary considerations.[2]

Contrary to the Examiner's position, Applicants note that a standard of "reasonable" predictiveness is an inappropriate consideration in and of itself in determining obviousness. Furthermore, in view of the pertinent art, Applicants note that there is absent a "reasonable expectation of success" as explained below.

The Examiner must first determine the scope and content of the prior art. Regarding the cited references, Sanchez and Uesugi are directed to *in vitro* studies of $\Delta^9$-tetrahydrocannabinol inducing apoptosis in C6 glioma cells. The Examiner incorrectly assumes that based on these teachings one skilled in the art would be motivated to extend the *in vitro* findings to *in vivo* treatment. To the contrary, one skilled in the art would not consider such treatments for glioblastomas to be reasonably applied *in vivo*. In fact, Applicants submit that these particular references teach *in vitro* results that are simply that and nothing more. They are *in vitro* results limited to *in vitro* findings. They are in no way indicative of *in vivo* treatment or success.

The Examiner must then ascertain the differences between the prior art and the claim in issue. Clearly, the cited prior art is limited in its teachings to *in vitro* assays. The claimed invention, on the other hand, is directed to *in vivo* treatments of glioblastomas.

Next, the Examiner must resolve the level of ordinary skill in the pertinent art, which Applicants submit is a primary issue. At the time of the filing of the application, Applicants submit that it was impossible to simply extrapolate *in vitro* teachings to *in vivo* treatment with any degree of expectation of success for glioblastomas. This assertion is based on teachings in the prior art that have long well established that *in vitro* studies of glioblastomas in particular cannot be used *in vivo* with any degree of success. While the Examiner has referenced various literature references that are purported to teach success in both *in vitro* and *in vivo* glioblastomas, the Examiner has simply ignored the numerous submissions by the Applicants that demonstrate the contrary -- the numerous failures of scientists in the art to use treatments *in vivo* based on *in vitro* studies. Applicants submit that the Examiner must consider the submissions by the Applicants as they establish that the state of the pertinent art demonstrates no reasonable predictive measure of success *in vivo*. In fact, these findings directly teach away from the Examiner's assertions.

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[2] *Graham v. John Deere,* 383 U.S. 1, 17-18, 148 USPQ 467 (1966).

Recall, Applicants provided ample support in this regard in the previously filed Declaration by Dr. Guzman (see Declaration as filed March 6, 2008). Applicants reiterate the various examples of the state of the art where glioblastomas could not be treated effectively *in vivo*. These include DNA alkylating agents such as nitrosureas, cisplatin and cyclophosphamide; antimetabolites such as methotrexate and fluorouracile; cytoskeleton inhibitors such as vinblatine and paclitaxel; topoisomerase inhibitors such as etoposide; or DNA intercalating agents such as doxorubicin. These specific compounds are discussed in further detail in the attached reference (Tab A: Castro et al. (2003)), which is listed on Dr. Guzman's CV (previously submitted). On page 75 of Castro et al., Table 2 discloses a listing of chemotherapeutic agents normally used to treat tumors, however, all such agents are ineffective to treat glioblastomas *in vivo*.

The simple fact is that the pertinent literature (now replete in the record) indicates that there is no reasonable expectation of success as purported by the Examiner. Furthermore, it appears that the Examiner fails to acknowledge that the state of the pertinent art, which teaches the specific and resistant nature of glioblastomas *in vivo* and demonstrates that brain tumors, in particular glioblastomas, are known to be resistant to chemotherapies as shown in the numerous references as submitted in the previously submitted Response of August 8, 2007. Applicants provide herewith further support for this premise at Tabs B-D, which further highly and support the resistance of glioblastomas.

As the state of the art has been well established, Applicants submit that the Examiner must also take into account secondary considerations. Such considerations include the clear long-felt need for successful treatment regimens as evidenced by the state of the art and lack of efficient *in vivo* treatment regimens for glioblastomas. Additionally, the inoperability of references must be considered. As explained above, the prior art teachings in no way lend themselves to operability in an *in vivo* setting. Furthermore, Applicants note that the Examiner has not recognized the unexpected results as shown in the Examples of the present specification. These Examples demonstrate the unexpected successful treatment of the claimed method *in vivo*. The results are unexpected due to the nature of glioblastoma's resistance to treatment.

For at least these reasons, Applicants submit that claim 16 is not obvious over the cited art. The Examiner has not met the burden of establishing a *prima facie* case of obviousness under 35 U.S.C. § 103(a). Accordingly, Applicants request that the rejection be withdrawn.

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below. If any fee is required in connection with this communication, or if any overpayment has been made, please charge any deficiency or credit any overpayment to Deposit Account No. 02-4377.

Respectfully submitted,

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Enclosures:

Tab A: Castro et al., "Current and future strategies for the treatment of malignant brain tumors", Pharmacology & Therapeutics 98: 71-108 (2003).

Tab B: Maher et al., "Malignant glioma: genetics and biology of a grave matter", Genes & Development 15: 1311-1333 (2001).

Tab C: Reardon et al., "Therapeutic Advances in the Treatment of Glioblastoma: Rationale and Potential Role of Targeted Agents", Oncologist 11: 152-164 (2006).

Tab D: King et al., "Gene Therapy and Targeted Toxins for Glioma", Current Gene Therapy 5(6): 535-557 (2005).